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EXAMINER	
POHNERT, STEVEN C	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,613	KUDARAVALLI ET AL.	
	Examiner	Art Unit	
	STEVEN C. POHNERT	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-19* is/are pending in the application.

4a) Of the above claim(s) *1-5,11-15 and 17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6,7,9,10 and 16* is/are rejected.

7)☒ Claim(s) *10* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/27/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to claims filed 3/16/2009 and arguments filed on 11/19/2008.

The amendment to the specification has overcome the objections to the specification.

The amendment to the claims has overcome the claim objections as the claims no longer refer to tables.

The amendment to the claims has overcome the written description rejection of claims 6-7 and 9-10. However, the written description rejection of claim 16 has been maintained for the reasons presented below.

The 102 of record has been withdrawn in view of the amendment of claim 16 to depend from claim 6.

Claim Objections

1. Claim 10 is objected to because of the following informalities: Amended claim 10 recites, "sesquestrant". This appears to be a typographical error and should be amended to recite "sequestrant. " Appropriate correction is required.

Ineffective incorporation by reference

2. The incorporation of essential material in the specification by reference to an unpublished U.S. application, foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference, if the material is relied upon to overcome any objection,

rejection, or other requirement imposed by the Office. The amendment must be accompanied by a statement executed by the applicant, or a practitioner representing the applicant, stating that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter. 37 CFR 1.57(f).

The attempt to incorporate subject matter into this application by reference to GenBank Accession X04500 (paragraph 10-13 of publication) is ineffective because the root words "incorporate" and/or "reference" have been omitted, see 37CFR 1.57(b).

Further 1.57(f) requires:

Any insertion of material incorporated by reference into the specification or drawings of an application must be by way of an amendment to the specification or drawings. Such an amendment must be accompanied by a statement that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter.

It is suggested that applicant amend paragraph 10 to recite "position 1423 of sequence X04500, which is incorporated by reference and is now SEQ ID NO 11 of the sequence listing." Similar amendments to paragraphs 11-13 should also clarify this issue.

The incorporation by reference will not be effective until correction is made to comply with 37 CFR 1.57(b), (c), or (d). If the incorporated material is relied upon to meet any outstanding objection, rejection, or other requirement imposed by the Office, the correction must be made within any time period set by the Office for responding to

the objection, rejection, or other requirement for the incorporation to be effective. Compliance will not be held in abeyance with respect to responding to the objection, rejection, or other requirement for the incorporation to be effective. In no case may the correction be made later than the close of prosecution as defined in 37 CFR 1.114(b), or abandonment of the application, whichever occurs earlier.

Specification

3. The amendment filed 3/16/2009 is objected to under 35 U.S.C. 132(a) because it introduces new matter into the disclosure. 35 U.S.C. 132(a) states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: the specification has added SEQ ID NO 11, by incorporation by reference to GenBank accession number X04500, but has not followed CFR1.157 as discussed above. Thus the amendment to the specification is considered to have added New Matter to the specification in view of the improper incorporation by reference.

Applicant is required to cancel the new matter in the reply to this Office Action.

Claim Rejections - 35 USC § 112-Maintained

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Enablement-Maintained

5. Claims 6-7, 9-10 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining whether a human patient is predisposed to cholesterol of 240 mg/dl in response to treatment with everolimus comprising obtaining a blood sample from patients, isolating genomic DNA from the sample, detecting a C at the -31 position of the IL-1B; detection of a C at position -31 of the IL-1B indicates that the human patient is predisposed to have a cholesterol of 240 mg/dl or more after 3 years of treatment with everolimus, does not reasonably provide enablement for determining the degrees of serum cholesterol elevation in treatment with rapamycin, everolimus, mycophenolic acid, mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus for any length of time The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is undue. These factors have been described by the court in re Wands, 8 USPQ2d 1400 (CA FC 1988). Wands states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in the Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the

invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The claim 6 is drawn to a method of determining the degree of serum cholesterol elevation which will occur in a human patient during treatment with an immunosuppressant by the nucleotide pair at the polymorphic site -31 T>C of IL-1β gene and assigning the patient to the a high cholesterol elevation group if both pairs are CG, assigning the patient to an intermediate elevation group if one pair is AT and one pair is CG and low cholesterol group if both pairs are AT, wherein said immunosuppressant is rapamycin, everolimus, mycophenolic acid, mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus.

Claim 7 is drawn to a method of treating human patient with immunosuppressive medication by determining the presence of a mutation at position -31 of IL-1b gene and treating the patient with one of rapamycin, everolimus, mycophenolic acid, mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus if both pairs are AT and with an alternative treatment if one of more of the alleles is GC.

Claim 9 draws the claims to immunosuppressive is everolimus.

Claim 10, draws the alternative treatment comprises the addition of a cholesterol lowering medication chosen from a bile acid sequestrant, a fibric acid derivative, an HMG-CoA reductase inhibitor, and nicotinic acid.

Claim 16 is drawn to the methods of determining the identity of the "any" nucleotide pair or haplotype comprises finding "any" SNPs any where in "any"

chromosome which are in "any" linkage disequilibrium to the polymorphism at -31of human IL-1b.

The amount of direction or guidance and the Presence and absence of working examples.

The specification teaches that El-Omar had previously identified the -31 mutation of the Il-1b promoter.

The specification teaches a study of male and female kidney transplant patients that are treated with everolimus (RAD) or mycophenolic acid and mycophenolate Mofetil (MMF) (see figure page 11).

The specification teaches that this study found 47 SNPs in 24 genes that were associated with increased cholesterol in patients treated with RAD (see last paragraph page 11). The specification continues that 21 of the 47 were determined not to be polymorphic (see last paragraph page 11). Two SNPs (-511 and -31) were found to be in the promoter of the Il-1b gene and showed a statistical correlation with increased cholesterol levels (see bottom page 11, to top of page 12). Thus the specification teaches mutations in the promoter of Il-1b were associated with elevated cholesterol in patients treated with RAD. This is not enabling for treatment with "any" immunosuppressive.

The specification continues, "Patients who were homozygous for the IL-1.beta. (-511) C>T base transition (T-T) or the IL-1.beta. (-31) T> C base transition (C-C) had the highest least mean levels of total cholesterol at their last visit regardless of treatment received during the study (p=0.0018 and p=0.0013 respectively). The

increase in total cholesterol levels was due to both increased levels of HDL and LDL: patients homozygous for the T allele at the (-511) position or the C allele at the (-31) position had the highest least square mean levels of HDL (p=0.0214 and p=0.0514 respectively) and LDL (p=0.0159 and p=0.0091 respectively) at their last visit. Importantly, however, the HDL to LDL ratios remained the same regardless of genotype. Therefore, our findings suggest that individuals homozygous for the T allele at position (-511) and homozygous for the C allele at position (-31) of the IL-1.beta. gene promoter may be predisposed to larger increases in total blood cholesterol" (see page 12 1st 3 paragraphs). Thus the specification teaches homozygous C at -31 is indicative of elevated cholesterol. The specification thus teaches patients with immunosuppressive who had the homozygous C at -31 were more likely to have higher cholesterol than those who did not. The specification does not teach the elevation is due to the immunosuppressive treatment, as the specification does not provide data for patients prior to treatment.

The specification in table 5 teaches that patients treated with RAD were statistically elevated regardless of IL-1b genotype (p=0.009), but those treated with MMF were not statistically elevated (p=0.0625). Table 5 further teaches that the effect of the RAD treatment group was great enough to make the combined MMF and RAD groups statistically significant regardless of -31 genotype (p=0.0013). Thus the specification teaches that RAD appears to increase cholesterol regardless of genotype.

The specification in table 7 teaches that patients treated with RAD were statistically elevated HDL regardless of IL-1b genotype (p=0.0205), but those treated

with MMF were not statistically elevated (p=0.1893). Table 7 further teaches that the effect of the RAD treatment group on HDL was great enough to make the combined MMF and RAD groups were not statistically significant regardless of -31 genotype (p=0.0514). Thus the specification teaches that RAD appears to increase HDL, irregardless of genotype.

The specification in table 9 teaches that patients treated with RAD were not statistically elevated HDL regardless of IL-1b genotype (p=0.143), but those treated with MMF were not statistically elevated (p=0.2061). Table 9 further teaches that the response is sample size dependent, but not genotype dependent as combined analysis of both groups, resulted in p=0.0091, however the individual groups is not statistically associated with increased LDL levels. Thus the specification teaches the IL-1b genotype is not predictably associated with LDL levels.

The specification teaches that CC or CT at the -31 position of the IL-1b promoter was statistically associated with cholesterol being greater than 240 mg/dl (p=0.0096) for treatment with RAD (see table 10).

The specification further teaches that a mutation at -31 disrupts the data box and thus inactivates transcription, thus decreasing transcription (see page 20, 3rd paragraph).

The state of prior art and the predictability or unpredictability of the art:

Moore et al teaches that treatment with immunosuppressant is commonly associated with persistent increases in total cholesterol (Drug Safety (2001) volume 24, pages 755-766) (see abstract). Moore et al teaches that immunosuppressant most

commonly associated with increased cholesterol are corticosteroids, calcineurin inhibitors, and rapamycin (see page 758, 2nd column 1st full paragraph). Moore teaches that in a European multicenter study demonstrated that 44% of patients on sirolimus had hypercholesterolemia (see page 759, 2nd column, 2nd paragraph). Moore teaches "Several lipid-lowering agents are available, but not all are appropriate for use in transplant recipients. Cholestyramine, for instance, may interfere with cyclosporine absorption, and nicotinic acid (niacin) may cause glucose intolerance, hyperuricaemia, and hepatotoxicity, as well as flushing. Fibric acid derivatives, such as gemfibrozil, have been shown to improve the LDL/HDL ratio in renal transplant patients and may have a role in recipients with hypertriglyceridaemia. However, they may not be suitable for use in liver graft recipients because of the potential to increase the incidence of gallstones" (see page 761), 2nd column, 1st paragraph).

The art teaches genetic variations and associations are often irreproducible. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing

conclusions from a single report of an association between a genetic variant and disease susceptibility.

The level of skill in the art:

The level of skill in the art is deemed to be high.

Quantity of experimentation necessary:

In order to practice the invention as claimed, one of ordinary skill in the art would firs have to determine if the presence of the -31 T>C polymorphism is indicative of any degree of cholesterol elevation. It would be unpredictable to associate any increased cholesterol levels with the -31 mutation in the human Il-1b gene as the specification teaches all patients irregardless of the -31 IL-1b genotype treated with everolimus (RAD) had increased cholesterol levels (table 5). Thus all -31 polymorphism IL-1b genotypes appear to be predictably associated with increased cholesterol when treated with everolimus (RAD). Further the specification teaches none of the patients treated with MMF alone had a statistical increase in cholesterol. Thus none of -31 polymorphism IL-1b genotypes appear to be predictably associated with increased cholesterol when treated with MMF. Thus the -31 polymorphism is not predictably associated with any increased cholesterol due to treatment with "any" immunosuppressive drugs.

Further it would be unpredictable to associate increased cholesterol with immunosuppressive treatment based on genotype when Moore teaches that increased cholesterol is a normal effect of cholesterol levels in patients treated with

immunosuppressive drugs. The specification does not provide any teachings as to the number of patients that did not have elevated cholesterol.

It would be further unpredictable to associate the -31 polymorphism with altered cholesterol levels as Wyllie teaches that the -31 has no functional effect on transcription and thus is not indicative of any disease state.

Further it would be unpredictable to treat any patient on immunosuppressive drugs with "any" alternative therapy as Moore teaches some alternative therapies interfere with absorption of the immunosuppressive drugs and/or have other negative side affects. Thus Moore teaches alternative therapies are not predictable in patients treated with immunosuppressants.

The teachings of Wylie that the -511 and -31 mutations described by the instant specification have no functional transcriptional affect, it would be unpredictable to associate any mutation on the chromosome with elevated cholesterol or the response to immunosuppressive agents.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, the negative teachings in the art, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

The response asserts on page 11 presents from the Non-final action:

> The specification thus teaches patients with immunosuppressive who had the homozygous C at -31 were more likely to have higher cholesterol than those who did not. The specification does not teach the elevation is due to the immunosuppressive treatment, as the specification does not provide data for patients prior to treatment.

The response asserts that applicant's have previously established on page 2 of the instant specification that everolimus and mycophenolic acid have a serious side effect of increased serum cholesterol levels. These arguments have been thoroughly reviewed but are no considered persuasive as the claims are not limited to everolimus and mycophenolic but encompass rapamycin, everolimus, mycophenolic acid, mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus. Thus the arguments are not commensurate with the scope of the invention. Further Matzkies (Transplantation proceedings (2002) volume 34, pages 1795-1796) teaches cyclosporine does not alter serum cholesterol levels. The teachings of Matzkies are being presented to refute the arguments of counsel and are not to be construed as new grounds of rejection.

The response notes that the Pediata Polska article does not teach treatment with any of the immunosuppressant drugs now required by the claims. The examiner has concurred by removal of the reference and arguments from the rejection.

The response concludes by asserting the instant claims are enabled and the rejection should be withdrawn. This argument has been thoroughly reviewed but is not considered persuasive as noted in the prior action Table 5 demonstrates that MMF

(Mycophenolic acid and mycophenolate mofetil) do not result in a statistically significant change in serum cholesterol regardless -31 IL-1b genotype (p=0.0625). Further tables 7 and 9 further demonstrate that the Il-1b -31 genotype is not significantly associated with a change HDL levels.

Thus as the specification nor prior art enable one of skill in the art to determine the degree of serum cholesterol elevation based on the human Il-1b genotype at position -31 the breadth of the claims are not enabled. While the specification is enabling for a method of determining whether a human patient is predisposed to cholesterol of 240 mg/dl in response to treatment with everolimus comprising obtaining a blood sample from patients, isolating genomic DNA from the sample, detecting a C at the -31 position of the IL-1B; detection of a C at position -31 of the IL-1B indicates that the human patient is predisposed to have a cholesterol of 240 mg/dl after 3 years of treatment with everolimus, does not reasonably provide enablement for determining the degrees of serum cholesterol elevation in treatment with rapamycin, everolimus, mycophenolic acid, mycophenolate mofetil, azathioprine, cyclosporine, or tacrolimus for any length of time

Written Description

Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims 16 is drawn to finding "any" SNPs on "a" chromosome that are in linkage disequilibrium with the SNPs of "any" IL-1b gene in "any" species. The claims do not set forth any a nucleic acid sequence for any chromosome.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been by full structure. The instant specification teaches SEQ ID NO 11 is human IL-1b gene. The specification does not provide the sequence information for haplotypes or SNPs on a chromosome that are in "any" linkage disequilibrium.

Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics (e.g. other nucleotide sequences or positions with in a specific gene or nucleic acid), specific features and functional attributes that would distinguish different members of the claimed genus. In the instant case the specification provides the no structural limitation for nucleotide pair or haplotypes which are in linkage disequilibrium with IL-1b position -31 on "any" chromosome. Thus as the specification does not teach a single nucleotide pair or haplotype comprising SNPs in linkage disequilibrium with containing IL-1b position -31, specification does not provide adequate written description for nucleotide pair in or haplotype pair in linkage disequilibrium with -31 polymorphism of human IL-1β.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The

specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and polymorphisms regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

In the instant application, the provided information regarding nucleic acid -31 polymorphism of Il-1b, do not constitute an adequate written description of the broad

subject matter of the claims, and so one of skill in the art cannot envision the detailed chemical structure of the nucleic acids encompassed by the claimed polymorphism. Adequate written description requires more than a statement that nucleic acids with a particular quality are part of the invention and reference to a potential method for their identification. The nucleic acid sequence is required.

In conclusion, the limited information provided regarding - nucleotide pair in or haplotype pair in linkage disequilibrium with -31 polymorphism of human IL-1β is not deemed sufficient to reasonably convey to one skilled in the art nucleic acid molecules claimed.

Thus, having considered the breadth of the claims and the provisions of the specification, it is concluded that the specification does not provide adequate written description for the claims.

Response to Arguments

The response asserts the amendment has overcome the written description rejection. The written description rejection of claims 6-7 and 9-10 has been overcome. The amendment did not address the rejection to SNPs in linkage disequilibrium. Thus the rejection is maintained.

New Matter

6. Claims 6-7, 9-10 and 16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 6-7, 9-10 and 16 are rejected as they recite "SEQ ID NO 11." SEQ ID NO 11 has been improperly incorporated by reference and thus is viewed as New Matter until the incorporation by reference issues are overcome.

112-2nd paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 6-7, 9-10 and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 6-7, 9-10 and 16 are indefinite over the recitation of "(position 1903 of SEQ ID NO 11)" because it is not clear if the phrase in parenthesis is a limitation of the claim.

Response to Arguments

The response asserts that the amendment of the claims has overcome the instant rejection. This argument has been thoroughly reviewed but is not considered persuasive as the amendment "(position 1903 of SEQ ID NO 11)" is still in parenthesis and the metes and bounds of the claims are thus unclear.

Summary

No claims are allowed.

Conclusions

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STEVEN C. POHNERT whose telephone number is (571)272-3803. The examiner can normally be reached on Monday-Friday 6:30-4:00, every second Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James (Doug) Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Steven Pohnert

/Juliet C Switzer/
Primary Examiner, Art Unit 1634